## REMARKS

The present Amendment is provided in response to the final Office Action mailed January 22, 2004. Claims 1-32, 34-36, 38-41, and 43-67 are pending, and claims 32, 34-36, 38-41, 43, and 64-67 are currently under consideration. Applicants note that claim 43 was canceled in the previous Amendment filed October 9, 2003, although this amendment is not reflected in the Disposition of Claims section of the Office Action Summary mailed January 22, 2004. By the present Amendment, claims 32 and 36 are amended solely for the purpose or providing additional clarity. Support for these amendments may be found throughout the specification and claims as originally filed, and, thus, these amendments do not constitute new matter. It should also be noted that the above amendments are made without prejudice to prosecution of any subject matter removed or modified by amendment in a related divisional, continuation or continuation-in-part application.

*Withdrawal of Rejections Under 35 U.S.C. § 102*

Applicants wish to thank the Examiner for his withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 32-35 and 39-41, as anticipated by WO 99/13816 (Moynihan), and the rejection under 35 U.S.C. § 102(e) of claims 32, 36, and 38-42, as anticipated by U.S. Patent No. 6,110,491 (Kirpotin), in light of the Amendment submitted October 9, 2003.

*Rejection Under 35 U.S.C. § 103 in View of Kirpotin*

Claims 38-41 and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin. Specifically, the Examiner alleges that Kirpotin discloses liposomal compositions comprising an active agent in precipitated form, wherein the liposome may comprise sphingomyelin and cholesterol, and the active agent is any compound with ionizable groups, including vincristine and vinblastine. The Examiner concedes that Kirpotin fails to teach camptothecins as the active agent. The Examiner, therefore, alleges that it would have been obvious to one of ordinary skill in the art to use vinca alkaloids with a reasonable expectation of success, since Kirpotin specifically suggests these agents.

As an initial matter, Applicants note some confusion and apparent discrepancies between the subject matter of the rejected claims and the Examiner's asserted basis of rejection. Specifically, the crux of the rejection is that it would have been obvious to one of ordinary skill in the art to use vinca alkaloids as the active agent, based upon the teachings of Kirpotin. However, while claim 38 is directed to vinca alkaloids, claims 39-41 are directed to camptothecins. Claim 43 is directed to both vinca alkaloids and camptothecins. Thus, the rejection of claims 38 and 43, as related to vinca alkaloids, and the rejection of claims 39-41 and 43, as directed to camptothecins, as being obvious in light of Kirpotin are addressed separately below.

Claims 39-41 and 43 Directed to Camptothecins

Applicants respectfully traverse the rejection of claims 39-41 and 43, directed to camptothecins, and submit that the Examiner has failed to establish a *prima facie* case of obviousness in light of Kirpotin. To establish a *prima facie* case of obviousness, the following three criteria must be met: (1) the prior art must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P., 8th Ed. § 2143. Claims 39-41 are each drawn to liposomal formulations comprising a camptothecin. This element is clearly not taught or suggested by Kirpotin, as acknowledged by the Examiner in the instant Office Action (page 2, lines 20-21). Accordingly, the Examiner has failed to meet the first criteria required to establish a *prima facie* case of obviousness.

In addition, Applicants submit that the Examiner has failed to demonstrate that the skilled artisan would be motivated to substitute a camptothecin for any of the drugs recited in Kirpotin with any reasonable expectation of success. While Kirpotin provides extensive lists of ionizable compounds that may be used according to their described invention, it does not recite camptothecins, or topotecan, specifically. Since this class of drugs was widely known at the time Kirpotin was filed, its exclusion from the lists of compounds provided by Kirpotin strongly suggests that Kirpotin did not believe that camptothecins could be used according to the described invention. The Examiner fails to remedy this deficiency of Kirpotin, by failing to

provide any factual support as to why the skilled artisan would believe that a camptothecin would be interchangeable with the ionizable compounds recited by Kirpotin with any reasonable expectation of success. Applicants note that the Examiner bears the burden of providing such factual support in order to establish a *prima facie* case of obviousness and that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991). Since the Examiner has not pointed to any teaching or motivation to use a camptothecin, it can only be concluded that the Examiner is impermissibly relying on the teachings of the instant application. Thus, the Examiner has not met the second or third criteria required to establish a *prima facie* case of obviousness.

In addition, Applicants submit that Kirpotin not only fails to provide any motivation for the skilled artisan to prepare a claimed liposomal topotecan formulation, but actually teaches away from the claimed compositions. Applicants note that Kirpotin teaches the loading of liposomes having different pHs at the interior and exterior of the liposomes, such that the drug being loaded is less soluble at the interior pH. Indeed, this is the mechanism utilized by Kirpotin to induce drug precipitation within the liposome. In marked contrast, the liposomes loaded by Applicants have an acidic interior pH, in which topotecan is more soluble than the less acidic exterior pH. The increased solubility of topotecan at acidic pH has been described in the art (Kearney *et al., Int. J. Pharm.* 127:229-237 (1996)). Accordingly, the skilled artisan would lack any motivation and have no reasonable expectation of successfully producing liposomal topotecan compositions of the invention, based upon the teachings of Kirpotin, which clearly indicate that the drug should be less soluble within the liposomes being loaded. Again, it is clear the Examiner has failed to meet the second and third criteria required to establish a *prima facie* case of obviousness.

Claims 38 and 43 Directed to Vinca Alkaloids

Applicants also respectfully traverse the rejection of claims 38 and 43, which are directed to vinca alkaloids, and submit that the Examiner has again failed to establish a *prima facie* case of obviousness in light of Kirpotin, since the Examiner has failed to demonstrate that Kirpotin teaches or suggests each element of the claimed invention. Specifically, Kirpotin fails

to teach or suggest liposomes comprising sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 35/50 mol%/mol% sphingomyelin/cholesterol, or in a 55:45 molar ratio, as recited in claims 38 and 43, respectively.

The skilled artisan would clearly appreciate that the specific lipid and other components of liposomes, and their relative amounts, are variable features of liposomes and can be important in determining the drug delivery properties of liposomes. As described in the instant specification, not all lipid formulations are equal for drug delivery purposes, and extensive research continues in an effort to identify formulations that demonstrate preferred characteristics for drug loading and storage, drug administration, pharmacokinetics, biodistribution, leakage rates, tumor accumulation, toxicity, and other features (paragraph 6). Furthermore, for certain drugs, including camptothecins, the field of liposomal drug delivery is further complicated due to dose-limiting toxicities. Accordingly, the identification and selection of a suitable liposomal vesicle with appropriate properties requires considerable effort and experimentation.

The present invention provides a liposomal formulation that comprises sphingomyelin and cholesterol at a ratio within a specific prescribed range and demonstrates that these liposomal formulations are effective in therapeutically delivering antineoplastic camptothecins using *in vivo* models of human disease (*e.g.*, Example 1). In contrast, while Kirpotin recites sphingomyelin in a long list of exemplary vesicle-forming lipids and makes passing mention that other lipid components, such as cholesterol, are known to contribute to membrane rigidity in lipid bilayer systems, Kirpotin fails to provide any teaching or suggestion of liposomes comprising sphingomyelin and cholesterol at the claimed ratios. Rather, the only liposomes specifically described by Kirpotin are composed of phosphatidylcholine, cholesterol, and polyethylene glycol derivatized distearolphosphatidyl ethanolamine at a molar ratio of 10:5:1, and contain the drug doxorubicin. Thus, Kirpotin clearly fails to teach or suggest the liposomes of the claimed liposomal formulations. In addition, Kirpotin provides absolutely no motivation for the skilled artisan to select the specific ratios of sphingomyelin and cholesterol recited in the instant claims. Accordingly, Kirpotin cannot render the claimed invention obvious.

In addition, Applicants submit that even assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness, the consideration of relevant secondary factors clearly establishes that the claimed liposomal compositions, comprising sphingomyelin and cholesterol, are not obvious in light of Kirpotin, alone or in combination with any other reference. Rather, the nonobviousness of the claimed invention is evidenced by the fact that the claimed liposomal formulations comprising sphingomyelin and cholesterol possess superior pharmocokinetic properties and related advantages as compared to other liposomal drug formulations, and that these advantages were unrecognized by Kirpotin. Specifically, the claimed liposomal compositions, composed of sphingomyelin and cholesterol, display superior retention of the encapsulated drug as compared to liposomal compositions composed of phosphotidylcholine, such as those described in Kirpotin. In addition, the claimed liposomal compositions provide greater levels of therapeutic agent in the subject's blood at various time points following administration.

As evidence of these unexpected advantages, Applicants file herewith the Declaration of Michael Hope, Ph.D., which details the surprising advantages of the presently claimed liposomal compositions. The Declaration provides evidence that the claimed liposomes, comprising sphingomyelin and cholesterol, have superior pharmacokinetic properties as compared to liposomes comprising DSPC and cholesterol, as described in the cited references. Specifically, liposomes comprising sphingomyelin and cholesterol showed significantly increased retention of topotecan as compared to liposomes comprising DSPC and cholesterol. Furthermore, liposomes comprising sphingomyelin and cholesterol also exhibited slower elimination from the plasma and provided increased plasma drug levels over time. Clearly, the claimed liposomal compositions possess superior characteristics that were not recognized by Kirpotin, which merely recited the possibility of using sphingomyelin but explicitly taught the use of phosphotidylcholine-based liposomes. Accordingly, Applicants submit that these surprisingly superior characteristics of the claimed compositions establish their non-obviousness over the cited prior art.

*Rejection Under 35 U.S.C. § 103 in View of Moynihan in Combination with Kirpotin*

Claims 32-36, 38-41, 43 and 64-67 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 (Moynihan) in combination with Kirpotin. Specifically, the Examiner alleges that Moynihan discloses liposomal formulations containing precipitated camptothecins and teaches that any phospholipid capable of forming liposomes and cholesterol can be used, although the Examiner concedes that Moynihan fails to teach the use of sphingomyelin. Rather, the Examiner asserts that Kirpotin teaches the use of sphingomyelin, so it would be obvious to one of ordinary skill in the art to use sphingomyelin, as taught by Kirpotin, in the liposomes of Moynihan or, alternatively, to use camptothecins, as taught by Moynihan, in the liposomes of Kirpotin, to achieve the claimed invention with a reasonable expectation of success.

Again, Applicants note a discrepancy between the subject matter of the rejected claims and the basis of rejection articulated by the Examiner. Specifically, the rejection relies upon the disclosure of camptothecins in Moynihan and, therefore, appears to be directed to claims reading on liposomal compositions comprising camptothecins. However, while claims 32, 34, 35, 39-41, 43 and 67 recite camptothecins, claims 36, 38, 43 and 64-66 recite vinca alkaloids. Nonetheless, in order to expedite prosecution of the instant application, this basis of rejection as applied to claims reciting camptothecins and claims reciting vinca alkaloids are addressed in turn below.

Claims 32, 34, 35, 39-41, 43 and 67 Directed to Camptothecins

Regarding claims 32, 34, 35, 39-41, 43 and 67, Applicants respectfully traverse this basis of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness. Specifically, the Examiner has pointed to no motivation or suggestion for the skilled artisan to combine the teachings of the references to produce the claimed formulations of liposomes comprising sphingomyelin and cholesterol and a camptothecin. Moynihan fails to even suggest that liposomal camptothecin formulations may be composed of sphingomyelin, and, therefore, clearly provides no motivation for the skilled artisan to use sphingomyelin to achieve the claimed invention. Kirpotin, as discussed above, merely recites sphingomyelin in a long list of phospholipids that might be used in forming liposomes comprising a precipitated

ionizable drug and fails to mention camptothecins at all. Nowhere does either reference suggest the specific combination of liposomes comprising sphingomyelin and cholesterol in combination with a camptothecin, as recited in the instant claims. Rather, combining the teachings of Moynihan and Kirpotin merely results in lists of potential liposomal components and drug compounds that might be combined in numerous alternative ways to produce any of a multitude of potential liposomal drug formulations, with no indication of which combinations might be used according to the inventions of either Moynihan or Kirpotin. Since it is well-established that obviousness can only be established when there is some teaching, suggestion or motivation to combine prior art references, and such teaching or motivation has not been demonstrated by the Examiner, a *prima facie* case of obviousness has clearly not been established.

Claims 36, 38 and 64-66 Directed to Vinca Alkaloids

Regarding claims 36, 38 and 64-66, Applicants respectfully traverse this basis of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the references, either alone or in combination, fail to teach each element of the claimed invention. As discussed in detail above, Kirpotin fails to teach or suggest liposomes comprising sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 35/50 mol%/mol% sphingomyelin/cholesterol, or in a 55:45 molar ratio, as recited in claims 38 and 43, respectively. Moynihan fails to remedy this deficiency, since Moynihan also fails to teach liposomes comprising sphingomyelin and cholesterol within the claimed ratios. Accordingly, this combination of references fails to teach each element of the claims, as required to establish a *prima facie* case of obviousness.

Furthermore, Applicants submit that the claimed liposomal compositions comprising sphingomyelin and cholesterol possess unexpected advantages over the specific liposomal compositions exemplified in Moynihan and Kirpotin, as described above and in the accompanying Declaration, and that these advantages are not recognized or acknowledged by either Moynihan or Kirpotin. Accordingly, the presently claimed invention, drawn to liposomal compositions comprising sphingomyelin and cholesterol and showing superior drug retention properties as compared to other liposomal drug formulations, cannot be obvious in light of the cited prior art references.

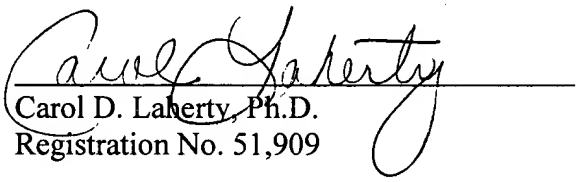
In light of these remarks and the accompanying Declaration establishing the existence of unexpectedly superior pharmacokinetic properties of the claimed liposomal compositions, Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants submit that all of the claims remaining in the application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. Should any issues remain, the Examiner is requested to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicants | : | Thomas D. Madden et al. |
| Application No. | : | 09/896,812 |
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DECLARATION OF MICHAEL J. HOPE, Ph.D.
PURSUANT TO 37 C.F.R. §1.132

I, Michael J. Hope, Ph,D. declare as follows:

1. I am a Principle Scientist in the Research group at Inex Pharmaceuticals, the assignee of the above-identified application (the "application") and have knowledge of the subject matter disclosed therein.

2. I am familiar with the content of the application, and I have reviewed the Office Action mailed January 22, 2004 and the prior art references cited therein, namely U.S. Patent No. 6,110,491 (referred to herein as "Kirpotin") and PCT Publication No. WO 99/13816 (referred to herein as "Moynihan"). I have reviewed data comparing the pharmacokinetic properties of liposomal compositions comprising

sphingomyelin and cholesterol, as claimed in the application, to liposomal compositions comprising phosphatidylcholine, as described in the prior art references, and I conclude that the compositions claimed in the application possess unexpectedly superior properties over those specifically exemplified in the prior art. The experimental data forming the basis of this conclusion are described below and graphically illustrated in attached Figure 1.

3. Liposomal compositions comprising either egg sphingomyelin (ESM) and cholesterol (CH) at a 55:45 molar ratio or 1,2 distearoylphosphotidylcholine (DSPC) and cholesterol (CH) at a 55:45 molar ratio were prepared and loaded with topotecan (Hycamtin™, SmithKline Beecham) using routine ionophore-mediated loading procedures, as described in U.S. Patent No. 5,837,282. [$^3$H]-cholesterylhexadecylether ([$^3$H]-CHE; Dupont) was included as a lipid marker. The initial drug-to-lipid ratios were 0.10 (w/w), and the external buffer consisted of 10 mM PBS, pH 7.5, and 300 mM sucrose.

4. The pharmacokinetic and drug leakage characteristics of the two different liposomal topotecan compositions were evaluated in ICR mice at various time points following intra venous administration of encapsulated topotecan (5 mg/kg topotecan) via the lateral tail vein. Total topotecan in blood was determined by a fluorescence assay after precipitation of plasma proteins with methanol. Topotecan was quantified by spectrofluorimetry at an excitation (2.5 nm slit width) and emission wavelength (2.5 nm slit width) of 380 and 518 nm, respectively. Lipid levels in plasma were determined by liquid scintillation counting of the [$^3$H]-CHE label.

5. Surprisingly, liposomes comprising ESM and CH showed significantly increased retention of topotecan as compared to liposomes comprising DSPC and CH at all time points examined, as shown in Figure 1. Approximately 50% of the topotecan was retained in the DSPC and CH liposomes at 2.5 hours, while approximately 50% of the topotecan was still retained in the ESM and CH liposomes at 6

hours. These data indicate that the liposomal compositions claimed in the application possess remarkably increased drug retention properties as compared to liposomes comprising phosphatidylcholine, as described in the prior art references.

6. Liposomes comprising ESM and CH also exhibited slower elimination from the plasma, as illustrated in Figure 2, and provided increased plasma drug levels over time, as illustrated in Figure 3. Notably, at four hours post-administration, approximately 40% of the topotecan provided in ESM and CH liposomes was still present in the plasma, whereas only 20% of the topotecan provided in DSPC and CH liposomes was still present in the plasma.

7. On the basis of these data, I conclude that the liposomal compositions claimed in the application offer unexpected advantages over other liposomal compositions, including liposomal compositions comprising phosphatidylcholine, as explicitly provided in the prior art references. Furthermore, I note that the advantages associated with the claimed liposomal compositions were not recognized or described in the prior art references and could not be predicted or expected based upon the teachings of these references.

I hereby declare that all statements made herein are, to my own knowledge, true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

Date July 21st, 2004.

M. J. Hope

Michael J. Hope, Ph.D.